Chapter 12

Treatment of large stage I-II lung tumors using stereotactic body radiotherapy: Planning considerations and early toxicity

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Abstract

Purpose
To study the dosimetric predictors of early clinical toxicity following SBRT in patients with lung tumors and planning target volumes (PTV) exceeding 80 cm$^3$.

Methods
18 consecutive patients who were treated using volumetric modulated arc therapy (RapidArc™) were assessed. All were either unfit or refused to undergo surgery or chemoradiotherapy. PTV planning objectives were as used in the ROSEL study protocol. Clinical toxicity was scored using Common Toxicity Criteria AE4.0. Lung volumes receiving 5, 10, 15, and 20 Gy ($V_5$, $V_{10}$, $V_{15}$ and $V_{20}$) and mean lung dose were assessed and correlated to symptomatic radiation pneumonitis (RP).

Results
Median age, age-adjusted Charlson-comorbidity score and PTV size were 74, 7.5 and 137 cm$^3$, respectively. At a median follow-up of 12.8 months, 8 deaths were recorded: 5 arising from comorbidity, 2 were potentially treatment-related and 1 had local recurrence. RP was reported in 5 patients (grade 2 in 3 and grade 3 in 2). All RP occurred in plans without a high priority optimization objective on contralateral lung. Acute RP was best predicted by contralateral lung $V_5$ (p<0.0001).

Conclusion
After SBRT using RapidArc in lung tumors >80 cm$^3$, the contralateral lung $V_5$ best predicts RP. Limiting contralateral lung $V_5$ to <26% may reduce acute toxicity.
Treatment of large primary tumors with SBRT

Introduction

In patients with medically inoperable stage I non-small-cell lung cancer (NSCLC), better clinical outcomes are seen with stereotactic body radiotherapy (SBRT) as compared to conventional fractionated radiotherapy [1]. Reported local control rates range from 88–92% although most studies report only outcomes for small tumors: nearly 90% of patients treated in some series had planning target volumes (PTV) smaller than 70 cm³ [2—4]. In contrast, local failure rates are higher in patients undergoing SBRT for lesions larger than 3 cm (T2) lesions [1]. In addition, lung tumors measuring 5 cm or larger also show a high incidence of distant failures, even after a complete surgical resection [5]. The high incidence of distant failure provides a rationale for our standard approach for treating patients with tumors >6 cm who are unfit to undergo surgery with concurrent chemoradiotherapy using conventional fractionation schemes.

Until 2008, SBRT for mobile tumors measuring >6 cm with SBRT was not technically possible at our center due to field size restriction on our designated linear accelerator (LINAC) [4]. In 2009, RapidArc™ (Varian Medical Systems, Palo Alto, CA) become our standard approach for SBRT of lung tumors as it allowed for plans with higher conformity, reduced chest wall doses and permitted faster SBRT delivery [6]. In patients with tumors >6 cm who were unfit to undergo surgery or chemoradiotherapy, or who refused conventional chemoradiotherapy, we implemented SBRT on newer linear accelerators as the prognosis using conventional radiotherapy alone was dismal.

However, the toxicity related to SBRT for larger tumors is not well described yet. In general, SBRT-related toxicity includes radiation pneumonitis (RP), bronchial stenosis or necrosis, esophageal injury, rib fractures and injuries to the brachial plexus [1]. Parameters shown to correlate with RP after conventional radiotherapy include lung volume receiving 5 Gy, 10 Gy, 13 Gy, 20 Gy and 30 Gy or mean lung dose (MLD) [7-10]. RP is uncommon after SBRT, but early reports suggested that tolerance values of 50% probability of lung toxic events are mean lung dose (MLD) of 1.2 Gy, and V₇ (volume of lung receiving 7 Gy or more) and V₁₀ values of 5.8% and 3.1% respectively [11]. The goal of this study was to evaluate the relevant dosimetric parameters and early clinical toxicity in patients with planning target volumes (PTVs) >80 cm³ treated with SBRT.
Materials and methods

Eighteen consecutive patients with stage I-II lung tumors without nodal metastases who had completed SBRT using RapidArc at the VU University Medical Center (VUmc) prior to December 31, 2009, and whose PTV was 80 cm³ or more were analyzed. Patients with synchronous non-pulmonary malignancies were excluded. Prior to referral for SBRT, patients were discussed in multi-disciplinary tumors board which included pulmonary oncologists and surgeons.

Patients were ineligible for surgical treatment or concurrent chemoradiotherapy due to comorbidities or patient refusal. SBRT for all patients was delivered as part of a routine clinical care within departmental protocols. All patients had solitary primary tumors and more than 3 months follow-up.

Details of our protocol for imaging and target definition have been described previously [6]. Briefly, patients were imaged and treated during uncoached quiet respiration. A single four-dimensional computed tomography scan 4DCT (GE Medical Systems, Waukesha, USA) was performed with the patient in a supine position with both arms above the head using an arm rest. No other fixation or immobilization device was used. The images were reconstructed in ten equally spaced time bins of 2.5 mm slice thickness using respiratory phase binning [12]. An internal target volume (ITV) was delineated, accounting for all tumor positions in the 4DCT dataset. The PTV was obtained by uniformly expending the ITV with a 5 mm margin.

The average intensity projection CT dataset was used for dose calculation and the contouring of all relevant organs at risk (OAR) such as the contralateral lung, spinal cord, chest wall, oesophagus, heart, and trachea. The chest wall adjacent to the tumor was contoured for each patient by including a volume of least 2 cm thickness extending from the pleura surface.

RapidArc plans were generated in the Eclipse treatment planning system, using a 6 MV photon beam. The first 7 patients were planned using Eclipse version 8.2.23, before a software upgrade to version 8.6.15 which permitted the use of an avoidance sector, i.e. defining a section of the arc without radiation delivery. The first two patients were treated on a Varian Trilogy accelerator equipped with a Millenium Multileaf Collimator (spatial resolution of 5 mm at isocenter) at a maximum dose rate of 600 MU/min. All other patients were treated on a Varian Novalis Tx accelerator equipped with a high definition Multileaf Collimator (spatial resolution of
2.5 mm at isocenter) at a maximum dose rate of 1000 MU/min. The collimator angles of all plans were set to 40° or 45°.

The planning objectives for the PTV were in accordance to those used in the ongoing ROSEL protocol which required that 95% of the PTV receives at least the nominal fraction dose, that 99% of the target volume receives ≥90% of the prescription dose, and that the maximum PTV dose is between 110% and 140% of the prescription dose [13]. Risk-adapted fractionation schemes of either 5 fractions of 11 Gy or 8 fractions of 7.5 Gy were used, depending on T stage and estimated risk of normal tissue toxicity [4]. All plans were normalized such that the nominal fraction dose corresponded to the 80% isodose. Dose was calculated using the Anisotropic Analytical Algorithm (AAA), accounting for tissue inhomogeneity, with a standard grid resolution of 2.5 mm [14].

All plans were delivered using at least 2 arcs for each fraction. During the optimization, the 2 different arcs plans were optimized sequentially, where the second arc refers to the dose distribution of the first calculated arc plan and compensates for any underdosage area in the PTV [15]. The final plan consisted of both the base dose plan and the second optimized plan. Sequential gantry rotations in clockwise and counter-clockwise directions were used to minimize the time between the arc deliveries. Treatment delivery was generally completed in less than 7 minutes [6].

Chest wall and mediastinum optimization objectives were individually set according to tumor location. When the PTV invaded any of the above OAR, upper optimization objectives limits were set to 80-90% of the prescription dose with high priority in order to ensure a rapid dose falloff at the PTV-OAR interface. For the first 5 patients, no optimization objective was applied to reduce the dose to the contralateral lung. With growing experience in planning such tumors, high priority optimization objectives were used for contralateral lung, often in combination with use of an avoidance sector or partial rotation arc, for the next 13 patients treated. For the other OAR such as trachea, esophagus, spinal cord, plexus, and heart, optimization objectives were applied if the OAR were in close proximity to the PTV in order to keep the final dose below values recommended in the ROSEL study. A 5 mm wide ring structure around the PTV was used as an additional OAR to ensure a rapid dose fall-off outside the PTV.
Patients treated on the Novalis Tx LINAC were set up using the Exactrac X-Ray 6D (BrainLAB, Heimstetten, Germany). During each treatment fraction, the patients were initially positioned using the infrared reflective markers of the ExacTrac system [16]. A cone-beam computed tomography (CBCT) scan was performed with the kilovoltage onboard imaging system, OBI (Varian Medical System, Palo Alto, CA). The images from CBCT scan were subsequently registered with the planning CT scan using the automatic soft-tissue match at the region of PTV plus 1 cm margin and were verified, and if necessary adapted, prior to treatment. The resulting discrepancies were corrected by the remote-controlled couch shift in all three directions, and couch rotation.

Routine clinical follow-up was performed every 3 months after treatment, with a diagnostic CT scan done at each visit. In frail patients who were unable to attend routine follow-up at our center, planned three monthly follow-up was performed by telephone, combined with information from the lung physicians or primary care providers. Clinical pneumonitis was assessed using the Common Terminology Criteria for Adverse Events, version 4.0 [17]. For any patients with incomplete follow-up data, hospital records were obtained and general practitioners were contacted to provide missing information.

Dosimetric data was abstracted from the planning system, and the mean and maximum PTV doses were reported. Plan conformity was expressed using the Conformity Index (CI). The CI80 corresponds to ratio of the total volume encompassed by 80% isodose line and the PTV volume receiving the same dose. The indices for CI60 and CI40 are similarly defined.

All reported lung doses refer to the volume of lung excluding the PTV. Mean lung dose (MLD), V5 (volume of “lung minus PTV” receiving 5 Gy or more), V10, V15, and V20 were assessed separately for the total lung, ipsilateral and contralateral lungs. For esophagus, heart and trachea, the maximum dose received by 1 cm³ (D1cm³) of the organ was recorded. For the chest wall, V45, V30, and V20 and the maximum dose to 2 cm³ (D2cm³) were assessed.

All statistical tests were two-sided with p \leq 0.05 indicative of statistical significance, and all statistical analyses were performed using the Statistical Package of Social Sciences (SPSS version 15.0, Chicago, USA)
Figure 1. Illustrative pre-treatment CT images for the first nine consecutive patients with large tumors (PTV indicated by an arrow).

Results

Fourteen patients had chronic obstructive airway disease (six having Global Initiative for Chronic Obstructive Lung Disease [GOLD] scores III or IV), 13 had cardiovascular diseases (including severe coronary artery disease, impaired cardiac function, peripheral vascular disease, or previous cerebrovascular events), two had renal failure, and one had undergone prior resection of 3 lung lobes for lung cancer. The median age-adjusted Charlson score was 7.5 (range 5-10). The median World Health Organization (WHO) performance score was 2 (range 1-3). Representative axial images from the first 9 patients are shown in Fig 1. The mean PTV volume
was 137 cm$^3$ (range 87-286 cm$^3$). Median treatment duration was 14 days (range 10-20 days). All patients tolerated the treatment and completed it uneventfully. The median follow-up after treatment was 12.8 months, determined using the reverse Kaplan-Meier method [18]. Clinical characteristics are summarized in Table 1.

Causes of death were obtained from hospital records, attending physicians, and family physicians. Two deaths were potentially treatment-related: a 65-year old man died of respiratory insufficiency associated with hemoptysis. Another death involved a 64-year old lady whose grade 3 RP responded poorly to steroid, and who subsequently requested euthanasia (Patient 4 in Fig. 1). Finally, an 84-year old man with pathologically confirmed local recurrence subsequently died of a pulmonary hemorrhage 10 months after SBRT (Patient 1 in Fig. 1). Five patients died of causes deemed unrelated to treatment: cerebral hemorrhage ($n=1$), complications of peripheral vascular disease ($n=1$), renal and heart failure ($n=1$), myocardial infarction in a patient whose tumors was not in the proximity of the heart ($n=1$), and collapse presumed to be of cardiac origin ($n=1$). Most deaths occurred in patients of age 80 or greater: five of seven patients in this age group died during the follow-up period.

The dose statistics for each structure averaged over all 18 patients are summarized in Table 2. The dose-volume histogram (DVH) analysis revealed that most plans fulfilled the acceptance criteria of the ROSEL randomized trial, although these constraints could not be met in all cases due to the large tumor sizes. For example, in a few cases, with PTV adjacent to the trachea or oesophagus, the dose-volume constraints recommended by the ROSEL study were not achieved.

Five patients (28%) developed RP: 3 had grade 2 pneumonitis and 2 had grade 3 pneumonitis. These five patients with RP were the first five in this study group, and all were planned without avoidance sector or optimization objective on the contralateral lung. One patient developed grade 2 esophagitis, and one patient with a large anterior tumor developed grade 2 edema of the breast and anterior chest wall (Fig. 2), both of which resolved with further follow-up. Two patients had grade 2 thoracic wall pain.
Table 1. Clinical and treatment characteristics for 18 patients with large stage I NSCLC tumors planned for stereotactic lung radiotherapy using RapidArc.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Median (range) or No. (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age</strong></td>
<td>74 (60-91)</td>
</tr>
<tr>
<td><strong>Gender</strong></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>6 (33%)</td>
</tr>
<tr>
<td>Male</td>
<td>12 (67%)</td>
</tr>
<tr>
<td><strong>FEV1 (Forced expiratory volume in 1 second)</strong></td>
<td>1.46 L (0.71-2.80 L)</td>
</tr>
<tr>
<td><strong>History of previous smoking</strong></td>
<td>18 (100%)</td>
</tr>
<tr>
<td><strong>Pathological confirmation (malign. or abn. cells)</strong></td>
<td>12 (67%)</td>
</tr>
<tr>
<td><strong>ITV volume</strong></td>
<td>75 cc (40-165 cm³)</td>
</tr>
<tr>
<td><strong>PTV volume</strong></td>
<td>137 cc (87-286 cm³)</td>
</tr>
<tr>
<td><strong>Major organs at risk</strong> (most patients had &gt;1)</td>
<td></td>
</tr>
<tr>
<td>Chest wall</td>
<td>14 (78%)</td>
</tr>
<tr>
<td>Spinal cord and vertebrae</td>
<td>7 (39%)</td>
</tr>
<tr>
<td>Esophagus</td>
<td>7 (39%)</td>
</tr>
<tr>
<td>Brachial plexus</td>
<td>3 (17%)</td>
</tr>
<tr>
<td>Ipsilateral pacemaker</td>
<td>3 (17%)</td>
</tr>
<tr>
<td>Other mediastinum including heart</td>
<td>11 (62%)</td>
</tr>
<tr>
<td><strong>Tumor location</strong></td>
<td></td>
</tr>
<tr>
<td>Central (≤ 2 cm from mediastinum)</td>
<td>13 (72%)</td>
</tr>
<tr>
<td>Peripheral</td>
<td>5 (28%)</td>
</tr>
<tr>
<td>Upper (above carina)</td>
<td>8 (44%)</td>
</tr>
<tr>
<td>Lower</td>
<td>10 (56%)</td>
</tr>
<tr>
<td><strong>Dose and Fractionation</strong></td>
<td></td>
</tr>
<tr>
<td>5 x 11 Gy</td>
<td>8 (44%)</td>
</tr>
<tr>
<td>8 x 7.5 Gy</td>
<td>10 (56%)</td>
</tr>
</tbody>
</table>
Figure 2. Grade 2 edema of the anterior chest wall and breast in a patient with a paramediastinal lung tumor treated with stereotactic radiation therapy. Left: radiotherapy plan, with planning target volume outlined in red and dose scale at left. Left: CT scan six months after treatment showing edema of the left breast and pectoralis.

Table 2. Summary of DVH-based analysis for PTV and OAR for 18 patients.

<table>
<thead>
<tr>
<th>Organ</th>
<th>Parameter</th>
<th>Average (Range)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PTV mean Dose relative to prescribed dose (%)</td>
<td>113 (110-119)</td>
<td></td>
</tr>
<tr>
<td>PTV max Dose relative to prescribed dose (%)</td>
<td>132 (122 – 140)</td>
<td></td>
</tr>
<tr>
<td>Max dose at 2cm (Gy)</td>
<td>41 (22 – 49)</td>
<td></td>
</tr>
<tr>
<td>CI 80%</td>
<td>1.08 (1.03 – 1.15)</td>
<td></td>
</tr>
<tr>
<td>CI 60%</td>
<td>1.84 (1.68 – 2.06)</td>
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<tr>
<td>CI 40%</td>
<td>3.92 (3.27 – 4.55)</td>
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</tr>
<tr>
<td>Total Lung - PTV</td>
<td></td>
<td></td>
</tr>
<tr>
<td>V_{20Gy} (%)</td>
<td>10 (2 – 18)</td>
<td></td>
</tr>
<tr>
<td>V_{15Gy} (%)</td>
<td>13 (3 – 21)</td>
<td></td>
</tr>
<tr>
<td>V_{10Gy} (%)</td>
<td>19 (6 – 42)</td>
<td></td>
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<tr>
<td>V_{5Gy} (%)</td>
<td>31 (15 – 59)</td>
<td></td>
</tr>
<tr>
<td>Ipsilateral Lung - PTV</td>
<td></td>
<td></td>
</tr>
<tr>
<td>V_{5Gy} (%)</td>
<td>44 (15 – 65)</td>
<td></td>
</tr>
<tr>
<td>Contralateral Lung</td>
<td></td>
<td></td>
</tr>
<tr>
<td>V_{5Gy} (%)</td>
<td>19 (0 – 51)</td>
<td></td>
</tr>
<tr>
<td>Spinal Cord, max dose</td>
<td></td>
<td></td>
</tr>
<tr>
<td>D_{max} (Gy)</td>
<td>16 (7 – 28)</td>
<td></td>
</tr>
<tr>
<td>Chest Wall</td>
<td></td>
<td></td>
</tr>
<tr>
<td>V_{45Gy} (cm^3)</td>
<td>31 (0 – 88)</td>
<td></td>
</tr>
<tr>
<td>V_{30Gy} (cm^3)</td>
<td>117 (0 – 238)</td>
<td></td>
</tr>
<tr>
<td>V_{20Gy} (cm^3)</td>
<td>222 (3 – 384)</td>
<td></td>
</tr>
<tr>
<td>D_{2cm}^3 (Gy)</td>
<td>56 (20 – 73)</td>
<td></td>
</tr>
<tr>
<td>*Esophagus, 1cc</td>
<td></td>
<td></td>
</tr>
<tr>
<td>D_{1cc} (Gy)</td>
<td>20 (9 – 36)</td>
<td></td>
</tr>
<tr>
<td>Trachea, 1cc</td>
<td></td>
<td></td>
</tr>
<tr>
<td>D_{1cc}^3 (Gy)</td>
<td>19 (0 – 68)</td>
<td></td>
</tr>
</tbody>
</table>

* Average for only 12 patients with PTV in close proximity to Esophagus
Fig. 3 shows the relationship between lung dose parameters and RP. Total lung V₅ and contralateral lung V₅ were the best predictors of RP, as all patients with total lung V₅>37% or contralateral lung V₅>26% developed pneumonitis, whereas none of the patients below these thresholds developed symptoms. Correlations with clinical symptoms were very strong and highly significant for both these variables (r>0.85, p<0.0001 for both). Ipsilateral lung V₅ correlated less strongly with clinical symptoms (r=0.66, p=0.004), as did mean lung dose (r=0.71, p=0.004) and total lung V₁₀ (r=0.58, p=0.01). Total lung V₁₅ and V₂₀ did not correlate with symptomatic pneumonitis (r<0.4, p>0.1 for both). PTV size also correlated with symptomatic pneumonitis (r=0.55 p=0.02).

The total lung V₅, V₁₀, V₁₅, V₂₀ were all inter-correlated (all r>0.6, and p<0.01), yet contralateral lung V₅ did not correlate significantly with ipsilateral V₅ or total lung V₁₀, V₁₅, or V₂₀, (all r<0.5 and p>0.05), suggesting that some alterations in contralateral lung V₅ may be achieved without substantially affecting the other dosimetric variables.

**Figure 3.** Relationship between dosimetric lung parameters and development of symptomatic radiation pneumonitis. Vₓ = volume of lung (%) receiving >X Gy; MLD: mean lung dose (Gy).
Discussion

Our study of early clinical toxicity after SBRT using RapidArc for lung tumors > 80 cm³ reveals that the contralateral lung V₅, total lung V₁₀ and V₅, MLD and the PTV size were all correlated with RP. The best correlation was observed for contralateral lung V₅, with all patients with a contralateral lung V₅>26% developing RP. Compared to our previous reports on post-SBRT lung treatments [4], this population of patients with larger tumors showed a higher rate of RP (28% vs. <10% in previous reports), a finding probably due to the larger size of the PTV treated in the current study. In addition, RP was highly influenced by the planning technique.

Unlike conventional radiotherapy, the unique fractionation schemes and dose distribution of SBRT have established a very distinctive clinical toxicity pattern [19]. Conversely, reliable dose-volume metrics as predictors for RP are lacking [20].

Previous studies on correlations between radiation pneumonitis (RP) and dosimetric parameters have occasionally shown conflicting findings. Although Fujino et al found no significant correlation between dosimetric factors and post-SBRT RP requiring steroids, doses lower than 20 Gy were not analyzed [21]. Takeda et. al. analyzed 128 patients with lung tumors post-SBRT and found no pretreatment clinical or dosimetric factors to be associated with RP grade ≥ 3 [22]. However, patients with RP grade 2 were excluded from their study. Yamashita et al reported RP grade ≥ 2 in seven of 25 patients after SBRT and reported that only the plan conformity index was significantly associated with the risk of RP, but other lung dose-volume metrics showed no significant correlation [23].

Several studies suggested that the mean lung dose (MLD) can predict for RP grade ≥ 2. Guckenberger et. al. analyzed 59 patients treated with SBRT for primary NSCLC and pulmonary metastases and reported that the MLD calculated for ipsilateral lung was the only factor significantly correlating with RP [24]. Similarly, Borst et al reported similar findings using MLD calculated over total lung volume excluding gross tumor volume [25]. However, doses to the contralateral lung alone were not analyzed in any of above mentioned studies.

The median size of PTVs investigated in our study was larger than those reported in similar studies (137 cm³ vs. < 45 cm³) [11, 21-25]. A study of lung density changes on follow-up CT scans of 50 patients post-SBRT revealed increases in Hounsfield Unit in areas receiving more than 6 Gy [26], which was greater in patients with large PTVs.
Our findings indicate that MLD had weaker correlation with RP, as well as $V_{10}$. Total lung and contralateral lung $V_5$ appeared to be the best predictors in which all patients with total lung $V_5 > 37\%$ and contralateral lung $V_5 > 26\%$ developed pneumonitis. Contralateral lung $V_5$ did not correlate significantly to any ipsilateral lung variables, suggesting that contralateral lung $V_5$ alone could predict the risk of RP instead of total lung $V_5$. This finding agrees with a current report suggesting that contralateral lung $V_5$ as an independent predictor for the development of $\geq$ grade 3 RP for patients with stage III lung tumors treated with conventional fractionation [27]. This correlation between contralateral lung dose and risk of RP can be explained by the possible functional compensatory changes in the contralateral lung due to ipsilateral lung radiation-induced injury [28]. As a result, sparing the contralateral lung may reduce the risk of RP.

Shorter treatment times for RapidArc have the advantage of reducing the likelihood of intra-fraction tumors displacements [29]. However, a trade-off of all forms of volumetric modulated arc therapies is that the low-dose regions are larger and more commonly involve the contralateral lung [6, 30]. The first five patients in this study group were planning without the use of avoidance sector, partial rotation arc or high priority optimization objective to limit the dose to contralateral lung and as a result, all had contralateral lung $V_5 > 26\%$. Subsequently, all these patients developed RP. Reassuringly, implementing an avoidance sector or high priority optimization objective on the contralateral lung effectively reduced the dose to the contralateral lung and led to no further cases of RP.

Limiting beams coming from contralateral direction by using avoidance sectors or partial rotation arcs can also be beneficial for the sparing of the mediastinal organs but a drawback is expected to be an increase in dose to the chest wall. Reported parameters for chest wall toxicity and radiation-induced rib fracture after SBRT are volume receiving $\geq 30\text{Gy}$ [31] or dose to $2 \text{cm}^3$ of the chest wall [32]. The latter publication suggested the correlation between $D_{2\text{cm}^3}$ and the probability of rib fracture, with the 5% and 50% risks given by total dose of 27.3 Gy and 49.8 Gy, respectively. By fitting our data with the adjustment for the biological effective dose for different fractionations, more than 80% of the patients had the likelihood of $>5\%$ risk of developing ribs fracture, and one patient was found to have $>50\%$ risk of developing ribs fracture. During our follow up, 2 patients had grade 2 chest wall pain but no ribs fracture has been reported. However, due to the limited follow up period and high involvement of the chest wall in the treatment field, more chest wall toxicity may be expected over time. Sparing of the
chest wall remains a challenge during the optimization. For the patient who developed edema of
the breast and anterior chest wall, the $V_{45}$ was the highest of all patients reported herein, but not
the $V_{30}$ nor $V_{20}$, reinforcing the importance of reducing high dose area outside the PTV.

Although our follow-up data were complete, a key limitation of our study is the short
follow-up time of all patients, a finding that is reflective of the frail patients who were referred
from other regions for treatment. The extensive non-cancer related co-morbidity profile of our
patients, as reflected by the median age-adjusted Charlson score of 7.5, makes this population
unsuited for studying late SBRT toxicity. However, a median follow up of 12.8 months deemed
to be sufficient for the detection of clinical RP as previous studies have demonstrated that RP
generally manifests at a median interval of 5 months post-SBRT [23-24]. The majority (72%) of
our patients had major cardiac co-morbidity, which in itself carries a poor prognosis: when
patients present with heart failure as a primary diagnosis, the 5-year all cause survival is only
24.4% [33]. Consequently, non-cancer mortality can mask the incidence of other subacute and
late toxicity, which in turn raises the issue as to whether SBRT should be offered to unfit patients
with larger stage I tumors when predictors of toxicity are not well established. Our routine
protocols accept such patients for treatment, since untreated stage I NSCLC is associated with 1-
and a 5-year survival of 49% and 4% respectively [34]. Furthermore, the alternative treatment of
primary surgery in patients with severe COPD is associated with an in-hospital mortality ranging
from 8-14% and local recurrence rate of 20-26% [35]. In view of the above findings, our routine
protocols have consistently accepted such high-risk patients and previous analysis revealed only
modest early toxicity when central tumors measuring $\leq 6$ cm were treated dose fractions of 7.5-11
Gy [36].

Early clinical toxicity patterns observed in this study highlight the importance of the
optimization technique in order to reduce RP. Longer follow up may assist the process of
treatment planning and hopefully to establish an acceptable dose-volume limit for each OAR.

**Conclusion**

SBRT using RapidArc is feasible for patient with stage I lung tumors $\geq 80$cm$^3$. Our results
suggest that contralateral lung $V_5$ is strongly correlated to RP and should be kept lower than
26%. We observed a higher risk of RP than previous studies, but the use of avoidance sectors
and high priority optimization objectives can effectively limit the dose to the contralateral lung,
thus, reducing the risk of RP. In the future, it is crucial to further characterize the dosimetric and clinical trade-offs in choosing an acceptable dose for each OAR (e.g. contralateral lung, mediastinal organs or chest) to create optimal treatment plans for patients with large tumors.

References


Chapter 13

Stereotactic lung radiotherapy: Do we need fiducial markers?

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